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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/650,726	08/29/2003	Chihiro Uematsu	1021.43085X00	9438

20457 7590 09/05/2006

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EXAMINER	
BABIC, CHRISTOPHER M	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 09/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/650,726	UEMATSU ET AL.	
	Examiner	Art Unit	
	Christopher M. Babic	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-11 and 13-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-11 and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 8-11 and 13-15 are pending. The following Office Action is in response to Applicant's response dated August 16, 2006.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 8-10 and 13-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Whitcombe et al. (WO 97/42345) as evidenced by Overbergh et al. (Quantification of Murine Cytokine mRNAs Using Real Time Quantitative Reverse Transcriptase PCR. Cytokine, Vol. 11, No. 4. April, 1999: 305-312)).

With regard to Claim 8, it is initially noted that the phrase --for gene expression analysis of genes derived from different samples-- is considered an *intended use* of the active method and does not incorporate a patentably distinguishable feature.

Whitcombe et al. disclose a method (Abstract; Page 1, Lines 20-23; Figure 17(a), (b); Page 20, Example 1, for example) comprising: (1) preparing first nucleotides

including a targeted gene by using a first sample and introducing a first base sequence and a second base sequence (Figure 17, Allele A Specific, for example), which are nonspecific to the base sequence of the targeted gene to the targeted gene so that the second base sequence is bound to a position closer to the 5' end than is the first base sequence (Figure 17, Allele A Specific; Page 4, Lines 22-25), *said first sample being derived from a first specimen* (i.e. normal cells, page 6, lines 10-20, for example) (2) preparing second nucleotides including the targeted gene by using a second sample and introducing a third base sequence and the second base sequence (Figure 17, Allele B Specific, for example), which are nonspecific to the base sequence of the targeted gene, to the targeted gene so that the second base sequence is bound to a position closer to the 5' end man is the third base sequence (Figure 17, Allele B Specific; Page 4, Lines 22-25), *said second sample being derived from a second specimen* (i.e. variant cancerous cells, page 6, lines 10-20, for example), mixing the first nucleotides and the second nucleotides (i.e. single tube genotyping infers mixing of the different sequences, allele A and B); (3) subjecting the first nucleotides and the second nucleotides to nucleic acid amplification using a primer comprising a base sequence specifically hybridizing to the targeted gene (Figure 17 (a),(b); Page 4, Lines 22-25), a primer comprising a base sequence identical to the second base sequence (Figure 17 (a),(b)) , a first probe comprising a base sequence identical or complementary to the first base sequence (Figure 17, Allele A Specific), and labeled at one end with a first fluorophore and at another end with a quencher (Figure 17; Page 2, Lines 23-29), a second probe comprising a base sequence identical or complementary to the third base sequence

(Figure 17, Allele B Specific), and labeled at one end with a second fluorophore and at another end with a quencher (Figure 17; Page 2, Lines 23-29), and thermostable DNA polymerase having 5'-3' exonuclease activity (Page 2, Lines 23-29, i.e. FRET); (4) digesting the first probe and the second probe bound to the first base sequence and the third base sequence, by the thermostable DNA polymerase at the time of the nucleic acid amplification (Page 2, Lines 23-29, i.e. FRET) ; (5) and detecting a fluorescence emitted by the first fluorophore and the second fluorophore released in digesting the first probe and the second probe, thereby assaying the amount of me product of the nucleic acid amplification (Page 2, Lines 23-29, i.e. FRET; Page 19, Lines 5-12, for example), *wherein a sequence of the targeted gene included in the first nucleotides and a sequence of the targeted gene included in the second nucleotides are the same* (figure 17; page 7, lines 5-20; page 10, lines 1-20; Page 20, Example 1, i.e. there is *a sequence* of the first sequence and *a sequence* of the second sequence, even as small as a sequence of dinucleotides, that are the same between the two target sequences *as a whole*, it is only the mutant nucleotides that are different between the two target sequences *as a whole*, for example).

With regard to Claim 9, Whitcombe et al. disclose diagnostic primers which are genome specific at their 3'-termini (i.e. "fourth base sequence) but which carry detector region and common extension tags (tags) at their 5'-termini (Page 4, Lines 22-25; Figure 17, for example).

With regard to Claim 10, Whitcombe et al. disclose that the nucleic acid sample may be DNA, RNA or reverse transcribed RNA (i.e. cDNA) (Page 9, Line 30-Page 10, Line 2).

Furthermore, Whitcombe et al. disclose their invention as being well suited for homogeneous assays and real time or end point analysis (Page 2, Lines 17-18). It is inherent to one of ordinary skill in the art that "real time or end point analysis" encompasses quantification of mRNA by using a reverse transcriptase PCR reaction to prepare cDNA for experimentation (For example, please see included reference: Overbergh et al. (Quantification of Murine Cytokine mRNAs Using Real Time Quantitative Reverse Transcriptase PCR. Cytokine, Vol. 11, No. 4. April, 1999: 305-312)).

With regard to newly added claims 13-15, it is noted that the specification *does not define* the terms "specimen" or "tissue" in any limiting manner. Thus, the terms "specimen" and "tissue" are extremely broad in nature and have been interpreted as such with regard to applicable prior art. For example, under a broad reasonable interpretation of the phrases "different specimen" or "different tissue", cancerous or malignant tissue can be considered to be of a different tissue or specimen than that of non-cancerous or benign even if taken from that same patient.

Thus, Whitcombe et al. disclose identifying variant sequences from *different tissue specimens* (i.e. cancerous cells in a background of normal cells) (Page 6, Lines 10-20, for example).

Response to Arguments - Claim Rejections - 35 USC § 102

Applicant's arguments with respect to the previously applied references have been fully considered but they are not persuasive.

Rejection of claim(s) 8-10 and 13-15 over Whitcombe

The crux of Applicant's arguments revolve around the assertion that Whitcombe et al. describes an expression analysis of two or more genes derived from one sample (that is, derived from one same sample). Applicant further submits that the method described in Whitcombe et al. is intended to be used for identifying a very small fraction of a variant sequence in a normal sequence or detecting the presence or absence of more than one suspected variant nucleotide in the same sample. Applicant further points to the diagnosis of cancer the expression analysis of Whitcombe et al. that is performed by a two-stage amplification procedure including a first stage to amplify any variant sequence that may be present using an Amplification Refractory Mutation System (ARMS) primer and a second stage to perform a genomic control reaction in the same reaction vessel using the same primers at low concentrations.

First, as noted above, the phrase --for gene expression analysis of -- is considered an *intended use* of the active method and does not incorporate a patentably distinguishable feature. In other words, only the active method steps of a process are examined with regard to applicable prior art. The fact that Whitcombe discloses their method as used for single-tube genotyping is irrelevant to the patentability of the instant invention. Whitcombe teaches *every* active method step of the instant invention.

Second, as noted above, the specification *does not define* the terms "specimen" or "tissue" in any limiting manner. Thus, the terms "specimen" and "tissue" are extremely broad in nature and have been interpreted as such with regard to applicable prior art. For example, under a broad reasonable interpretation of the phrases "different specimen" or "different tissue", cancerous or malignant tissue can be considered to be of a different tissue or specimen than that of non-cancerous or benign even if taken from that same patient. Thus, Whitcombe et al. disclose identifying variant sequences from *different tissue specimens* (i.e. cancerous cells in a background of normal cells)

Finally, with regard to the supplementary limitation added to the end of claim 8, the phrase "a sequence" encompasses sequences as short as even a dinucleotide. Thus, Whitcombe cleary teaches *a sequence* of the first sequence and *a sequence*, of the second sequence, even as small as a sequence of dinucleotides, that are the same between the two target sequences *as a whole*; it is only the mutant nucleotides that are different between the two target sequences *as a whole*, for example).

Thus, the rejections are maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Whitcombe et al. (WO 97/42345), in view of Shah et al. (U.S. 6,165,723).

With regard to Claim 5, the methods disclosed by Whitcombe et al. are outlined in the above rejections. Whitcombe et al. does not specifically teach a multiplex assay with multiple probes having substantially the same T_m value.

Shah et al. disclose an in situ hybridization method for detecting target nucleic acids, wherein for simultaneous detection the oligonucleotides which are specific for the different nucleic acids commonly present in the clinical specimen can be designed such that the T_m values of all probe complex sequences are very similar (Abstract; Column 5, Lines 1-18). In addition, Shah et al. disclose several advantages of their methods, such as reduction hybridization time (Column 5, Lines 58-67).

One of ordinary skill in the art would have been motivated to use the probes disclosed by Shah et al. in the diagnostic amplification methods disclosed by Whitcombe et al. for among other advantages, a reduction in hybridization time. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods.

Response to Arguments - Claim Rejections - 35 USC § 103

Applicant's amendments and arguments with respect to the previously applied references have been fully considered but they are not persuasive. Please see response above.

Conclusion

Claims 8-11 and 13-15 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

8/25/06

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8/31/06